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(71) Applicant

Sandoz Ltd.

(Switzerland),

35 Lichtstrasse,

CH—4002 Basle,

Switzerland

(72) Inventors

Thomas Kissel,

Reinhardt Bergauer

(74) Agent and/or Address for
Service

B. A. Yorke and Co.,

98 The Centre, Feltham,

Middlesex TW13 4EP

(54) Sustained release layered
pharmaceutical compositions

(57) The present invention provides a
sustained release buccal
pharmaceutical composition
comprising

i) a non-adhesive water-soluble or
disintegrable layer

ii) an adhesive layer capable of

adhering to the mucous membrane of
the mouth, and

iii) a medicament in at least one of
said layers
characterised in that the outer surface
of the adhesive layer is conformable or
conforms to the mucous membrane of
the mouth. Visual identification means
(e.g. colouring) may be present in one
of the layers.

GB 2 108 841 A

SPECIFICATION

Sustained release pharmaceutical compositions

This invention relates to sustained release pharmaceutical compositions, especially for buccal use, i.e. in any part of the mouth.

5 Sustained release pharmaceutical compositions are designed to produce a uniform and continuous release of medicament over a long period of time, thereby avoiding the necessity of frequent administration of the medicament. 5

Certain sustained release pharmaceutical compositions for adherence to the oral mucous membrane are known. The medicament if systemically active passes directly through the oral mucous 10 membrane into the blood stream. Alternatively the medicament may be locally active against disorders in the mouth. In one proposed buccal bandage strip there is provided a medicament reservoir and a pressure sensitive adhesive layer which sticks the strip onto the mucous membrane of the mouth or gum. The reservoir contains the medicament, e.g. on oxytoxic drug, in microencapsulated form, in a film 15 formed from a polymer such as polyvinylacetate which is completely insoluble and does not become porous on contact with the oral mucous yet is permeable to passage of the medicament through the film when the buccal strip is applied to the inside of the mouth. 15

These pharmaceutical compositions are, however, complicated in construction. Often they do not exhibit satisfactory release and bioavailability characteristics for many types of medicaments. Moreover, the medicament reservoir tends to dispense only a small proportion of the medicament in the film.

20 The recently published European Patent Publication No. 20777 and UPS 4,292,999 propose a sustained release pharmaceutical composition in the form of a pressed tablet with flat upper and lower surfaces and having two layers one of which is a non-adhesive layer which is either water-soluble or water-disintegrable and an adhesive layer which adheres to a mucous membrane and which swells on contact with water. 20

25 Such compositions may suffer from disadvantages. For example the tablets may not stick securely onto the oral mucous membrane, especially if the tablets are of sufficient size to incorporate large amounts of medicament to provide a satisfactory sustained action over a long period. Moreover the tablets can cause discomfort when they are stuck to the oral mucous membrane. 25

30 Furthermore there is no way of visually distinguishing between the non-adhesive layer and adhesive layer and this may be inconvenient in practice. 30

After exhaustive testing of many systems for buccal administration of medicaments we have produced buccal pharmaceutical compositions having interesting release properties, of simple construction, and suitable for widespread use.

35 In one aspect the present invention provides a sustained release buccal pharmaceutical composition comprising 35

(i) a non-adhesive water-soluble or disintegrable layer,
(ii) an adhesive layer capable of adhering to the mucous membrane of the mouth, and
(iii) a medicament in at least one of said layers characterised in that the outer surface of the 40 adhesive layer is conformable or conforms to the shape of the mucous membrane of the mouth to which the composition is to be applied. 40

In another aspect the present invention provides a sustained release buccal pharmaceutical composition comprising

(i) a non-adhesive water-soluble or disintegrable layer,
(ii) an adhesive layer capable of adhering to the mucous membrane of the mouth, and 45 (iii) a medicament in at least one of said layers 45

characterised by visual identification means in or on the adhesive layer or non-adhesive layer. Conveniently the outer surface of the adhesive layer is shaped to be inwardly concave to fit onto the outside surface of the gum. Preferably the outer surface of the non-adhesive layer is outwardly 50 convex. 50

The exact radius of curvature will depend on the mucous membrane to which the pharmaceutical composition according to the invention is to be applied. Preferably the pharmaceutical compositions according to the invention are to be applied to the interior surface of the gum near the upper large molar teeth.

55 Suitably the adhesive layer is identified by being coloured differently from the non-adhesive layer. The pharmaceutical compositions may be formulated as described in European Patent Publication No. 20777 and USP 4292999, the contents of which are hereby incorporated by reference. Preferably the pharmaceutical compositions are produced by compressing a granulate in a shaped die to produce a tablet with suitable curved surfaces. Alternatively and preferably the pharmaceutical compositions may be in the form of a flexible film strip. 55

60 We have now found that a particularly suitable buccal pharmaceutical composition is a buccal strip pharmaceutical composition comprising 60

(i) a non-adhesive polymer film layer which is porous on contact with, and wettable by, oral mucous.

(ii) an adhesive layer capable of adhering to the inside of the mouth, and

(iii) a medicament dissolved or dispersed in at least one of said layers.

The constituents of the non-adhesive layer, especially the polymer, should conveniently be chosen so as to dissolve slowly, but not too quickly otherwise a satisfactory sustained release action will not be obtained. It is desirable that the non-adhesive layer will dissolve over 5 to 24 hours.

5 The non-adhesive layer may be formed from any suitable polymer, e.g. acrylic polymers and copolymers, hydrophilic vinyl polymers, polysaccharides, etc. 5

Suitably the non-adhesive layer is formed from a cellulose derivative, which is capable of forming suitably porous films as determined by conventional means, e.g. by electromicroscopy. Cellulose derivatives that come into question include methylcellulose (e.g. the brand Methocel), ethylcellulose 10 (e.g. the brand Ethocel) and preferably hydroxypropylcellulose (e.g. the brand Klucel). 10

Preferred hydroxypropylcellulose polymers are those produced by reacting alkali cellulose with propylene oxide, see e.g. p. 307 et seq. in Encyclopedia of Polymer science and Technology, Vol. 15, Supplement 1973, and having a Bookfield viscosity of 4000 to 6500 at 2% concentration in water.

If desired the film may contain a softener, e.g. a hydrophilic softener in concentration of from 15 about 5 to about 30% by weight in order to provide a film of appropriate flexibility and pliability to bend and fit easily into the mouth and to produce a satisfactory release of medicament. A suitable softener is polyethyleneglycol (MW 100—500) or glycerine triacetate such as triacetin. 15

Naturally other types of polymers and excipients can be included in the pharmaceutical compositions of the invention so long as the resultant composition is disintegrable, dissolvable, or 20 porous on contact with, and wettable by, oral mucous. 20

Any acceptable adhesive may be used in the adhesive layer. A suitable adhesive is an appropriate water-soluble cellulose gum, e.g. sodium carboxymethylcellulose.

Any medicament may be used. Preferably the medicament is used in a form which is sufficiently stable in the oral mucosa. For example we have found that for pharmaceutical compositions according to 25 the invention the medicament should be stable to slightly acid conditions, e.g. pH 5.8. 25

The medicament is preferably sufficiently active such that the pharmaceutical compositions according to the invention may be formulated to be a reasonable size yet contain sufficient amount of active agent to provide a prolonged duration of action.

For the pharmaceutical compositions according to the invention it is preferred that the 30 medicament is in a form with an acceptable taste or which is tasteless. The pharmaceutical compositions according to the invention are especially indicated for the administration of medicaments locally therapeutically active against disorders of the mouth. 30

Alternatively the pharmaceutical compositions of the invention are especially indicated for the administration of medicaments which are not satisfactorily administered orally, e.g. because of bad 35 absorption from the gastro-intestinal system, or because of a high first pass effect. 35

Typical medicaments contemplated for use include vasoconstrictors, vasodilators, beta-blockers, calcium antagonists, vigilance-increasing agents, anti-migraine agents, analgesics, anti-pyretics, local anaesthetics, anti-parkinson agents, anti-obesity agents, sympathomimetic agents, diuretics, anti-histamines, analeptics, anti-hypertensives, anti-biotics, anti-inflammatory agents, mytonolytics, CNS 40 stimulants, anti-depressants, neuroleptics, tranquillizers, anti-aggressive agents, anti-asthmatics, anti-diabetic agents, anti-convulsants, prolactin inhibitors, cardiotonics and hormones. The medicament may be locally active or systemically active. The medicament may be for example a vasodilatory nitrate. 40

The pharmaceutical compositions according to the present invention have given especially interesting and surprising release and bio-availability characteristics when the medicament is an ergot alkaloid, e.g. 45 such as an ergot cyclic peptide alkaloid wherein the lysergic acid moiety may be optionally hydrogenated in the 9, 10 position. The preferred ergot alkaloid is codergocrine. Alternatively it may be ergotamine, dihydroergotamine, bromoergocryptine, methyllysergide or methylergobasine. It is also preferred to use a betablocker as active agent, for example, plndolol, mepindolol etc. Other preferred 50 medicaments include e.g. dihydropyridine, calcium antagonists, e.g. 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-pyridine-3,5-carboxylic acid diethyl ester, or 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridinecarboxylic acid isopropyl ester, or 4-(2,1,3)-benzothiadiazol-4-yl-1,4-dihydro-2,6-dimethyl pyridine-3,5-carboxylic acid methyl ester. 50

Preferably the medicament is micronized. If desired the medicament may be in pharmaceutical acceptable acid addition form. 55

55 The pharmaceutical compositions according to the invention may contain other hydrophilic pharmaceutical additives, e.g. flavouring agents, sweetening agents and other agents to mask any unpleasant taste of the medicament, preservatives etc.

The pharmaceutical compositions according to the invention may be any desired thickness. It is preferred to use a non-adhesive layer from 0.1 to about 5 mm thick, e.g. from 0.2 to 1.7 mm, and an 60 adhesive layer of from about 0.05 to about 0.5 mm thick e.g. about 0.08 mm thick. The individual pharmaceutical compositions according to the invention may be of any desired shape and dimensions. It is preferred to use a rectangular film strip of about 1 cm x about 3 cm with rounded corners. 60

Pharmaceutical compositions according to the invention may be produced as described in European Patent Publication 20777 and USP 4,292,999.

65 The strip pharmaceutical compositions according to the invention may be prepared in 65

conventional manner in a batch or continuous drawing, melt, solvent coating or spraying process. The layers may be built up in several stages. If desired the non-adhesive film layer may be built up in several stages. The adhesive layer may be formulated as the last stage.

- Alternatively the adhesive layer may be formed first and the non-adhesive film layer built up on the adhesive layer. The process of forming the individual layers may be effected in analogous manner to that described in UK Patent Specification 1,510,999, which exemplifies mono-layer foils for oral or vaginal administration. In one simple batch process, the components of the film layer may be dissolved or suspended in a volatile solvent producing a highly viscous liquid which is then spread onto a flat surface e.g. a siliconized glass plate. The solvent should naturally be chosen such that any residue is pharmaceutically acceptable. Suitable solvents include acetone and ethanol. The solvent may be allowed to evaporate off at room temperature or at a slightly elevated temperature. If desired the film layer is built up in several stages. The components of the adhesive layer in an appropriate solvent such as water may be spread on top of the film layer and the solvent allowed to evaporate.
- The resultant film is then removed, e.g. with a spatula, optionally after pre-treatment of the film with dry ice to facilitate removal. The film is then cut up into strips. Each strip may then be packed into a flexible protective container made from e.g. aluminium foil.

- The preferred amount and concentration of medicament in any particular pharmaceutical composition according to the invention will naturally depend on, inter alia, the release characteristics of the pharmaceutical composition, the dimensions of the pharmaceutical compositions, and the potency and characteristics of the medicament and the period of the time the pharmaceutical composition is to be used. In general a buccal pharmaceutical composition for once-a-day application may contain from about 0.1 to 10, e.g. 1 to 10 times, the total daily dosage of the medicament. Preferably the amount of medicament is less than 50 mg per pharmaceutical composition, more preferably less than 20 mg. A suitable dose is about from 1 to 10 mg in the case of an ergot alkaloid such as those mentioned above.
- The medicament suitably comprises from about 0.1 to about 5% of the total film weight. Preferably the medicament is in the non-adhesive layer.

When the medicament is dispersed throughout the pharmaceutical composition of the invention, the particle size of the medicament is conveniently less than 50 microns.

- In use the buccal pharmaceutical composition according to the invention is stuck to the outside, or inside, of the gum particularly near the large molar teeth by way of the adhesive layer. It has been found that the pharmaceutical composition according to the invention will generally stay in place and cause the minimum of inconvenience, even during smoking, drinking or eating.

The following examples illustrate the invention.

- In the examples
- (1) Co-dergocrine mesylate is micronized: particle size $< 50 \mu\text{m}$ diameter. Pindolol is similarly micronized.
 - (2) HPC is hydroxypropylcellulose, brand Klucel LF obtainable from Hercules, USA.
 - (3) Triacetin is glycerine triacetate.
 - (4) NaCMC is sodium carboxymethylcellulose brand 7MF from Hercules, USA.
 - (5) The lemon flavour is Tetrarome Aroma (liquid).
 - (6) Ethylcellulose is brand ethocel from Dow, USA.

- Further information on the ingredients are available in H. P. Fiedler, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, Editio Cantor, Aulendorf, W. Germany, 2nd Edition, 1981, as well as from the manufacturers specified above, e.g. Klucel brochure on Chemical and Physical properties, 1976, produced by Hercules.

EXAMPLE 1: Co-dergocrine film strips
Composition of film

	Constituents	Per Strip (1 x 3 cm) mg	Per charge g	
5	Film layer			5
	Co-dergocrine ⁽¹⁾ mesylate	4.5	3.19	
	HPC ⁽²⁾	186.9	156.76	
	Triacetin ⁽³⁾	60	50.174	
10	FD + C Blue No. 2 (Colour)	0.24	0.21	10
	Adhesive layer			
	NaCMC ⁽⁴⁾	47.9	40	
		<u>299.54</u>	<u>250.434</u>	

15 PREPARATION

One charge of the components of the film layer was stirred in 600 ml of acetone/ethanol (1:1) to provide a highly viscous mixture. This mixture was poured onto a glass plate the surface of which had been siliconized by treatment with dimethylpolysiloxane and o-xylene (1:10), heated to 240°C for 5 hours and then cooled. A spreader 3 mm above the surface of the glass plate was drawn across the mixture to form a flat layer. The mixture was allowed to dry for 48 hours at room temperature to yield a film layer (ca. 0.291 mm thick).

40 g of NaCMC is dissolved in 1 litre of water. The liquid is applied to the film layer and allowed to dry to yield an adhesive layer ca. 0.082 mm thick. The resultant film is treated with dry ice to cool it and then removed with a spatula.

25 The film is cut up into strips 1 cm x 3 cm (ca. 300 mg in weight) and having rounded edges. In use a buccal strip is stuck to the outside of the upper gum of the mouth.

The buccal strip composition was administered to 6 healthy subjects. Results obtained were:—

	Time (hrs)	Blood plasma (ng/l)	Urine (% of dose)	
30	2	0.09 (± 0.03)	—	30
	4	0.26 (± 0.06)	0.09 (± 0.03)	
	6	0.33 (± 0.08)	—	
	8	0.32 (± 0.06)	0.35 (± 0.06)	
	24	0.07 (± 0.02)	0.69 (± 0.11)	
35	48	—	0.82 (± 0.13)	35

As can be seen a significant retardation is observed.

EXAMPLE 2: Pindolol film strips

In analogous manner to that described in Example 1, 300 mg buccal strips containing pindolol with the following compositions have been made:—

5	Constituents	Amount per strip in mg		5
		(a)	(b)	
	Film layer			
	Pindolol (free base)	5.6	4.74	
	HPC ⁽²⁾	232.9	75.81	
	Ethylcellulose ⁽⁶⁾	—	94.82	
10	PEG 200	—	18.97	10
	Sodium Saccharin	—	1.27	
	Lemon flavour ⁽⁵⁾	1.5	1.27	
	Adhesive layer			
	NaCMC ⁽⁴⁾	59.7	101.15	
15	Tartrazine	0.3	0.07	15
	(FD + C No 5)			
	Sodium Saccharin	—	0.64	
	Lemon flavour ⁽⁵⁾	—	1.26	

EXAMPLE 3: Co-dergocrine film strips

The following compositions have been made:—

20	Constituents	Per strip	Per charge	20
		mg	g	
	Adhesive layer			
	NaCMC ⁽⁴⁾	32.6	80	
25	Tartrazin	0.16	0.4	25
	(F D + C Yellow 5)			
	Film layer			
	HPC ⁽²⁾	381.64	936.3	
	Co-dergocrine	4.5	11	
30	mesylate ⁽¹⁾			30

PREPARATION

The charge of the adhesive layer components was dissolved in 2000 ml 40% ethanol. Half of this mixture was then spread onto a glass plate prepared as described in Example 1 and to provide a flat dry layer in a manner analogous to that described in Example 1. The procedure was repeated with the rest of the mixture to increase the thickness of the adhesive film layer, which was allowed to dry.

A charge of the film layer components (first the co-dergocrine and then the HPC) is dissolved in acetone/ethanol; 1:1 4200 ml). A quarter of this mixture is then spread onto the adhesive layer, and in analogous manner to that described in Example 1 to provide a film layer which was dried overnight. The procedure was repeated three times using up the rest of the mixture to increase the thickness of the film. The film was finally dried for 2 days.

The film layer is cup up into buccal strips (1 x 3 cm) each of weight 418.90 mg and of thickness 1.1625 mm.

RATE OF RELEASE OF ACTIVE AGENT:

Six strips were each exposed to 5 ml of aqueous stirred phosphate pH 5.8 buffer and the amount of active agent released into the buffer was measured spectrophotometrically.

	Time (minutes)	Release %	Standard Deviation %	
	15	4.6	0.8	
	30	6.4	0.8	
5	60	11.4	1.5	5
	120	19.8	3.5	
	180	29.2	3.6	
	240	36.8	6.0	
	300	45.8	6.1	
10	360	54.1	8.4	10

As can be seen a steady release of about 10% of the active agent per hour is observed.

EXAMPLE 4: Pindolol film strips

	Constituents	Per Strip mg	Per Charge g	
15	Adhesive layer NaCMC ⁽⁴⁾	32.6	80	15
	Indigocarmine (F D + C Blue No 2)	0.16	0.4	
20	Film layer HPC ⁽²⁾	381.64	936.3	20
	Pindolol (base)	15	38.0	

In the same manner as that described in Example 3, buccal strips of weight 418.9 mg and thickness 1.625 mm were produced.

Rate of release of active agent (in analogous manner to Example 3)

	Time (minutes)	Release %	Standard Deviation %	
25	15	10.9	0.6	25
	30	13.9	0.9	
	60	19.3	1.4	
30	120	27.8	2.2	30
	180	35.9	2.8	
	240	44.8	3.9	
	300	51.9	5.3	
	360	59.6	6.7	

CLINICAL TRIAL

A cross-over trial was effected with 6 healthy subjects using a 15 mg buccal strip and a 15 mg normal tablet. With the buccal strip there was a delay of 1—2 hours before pindolol could be detected in the blood plasma.

- 5 Additionally the maximum amount of drug in the plasma was reached significantly later than with the normal tablet. Bioavailability of the buccal strip as indicated by the AUC (Area under the curve) of the amount of the drug in the plasma was about 65% that of the normal tablet.

EXAMPLE 5: Pindolol film strips

Composition

10	Constituents	Per strip (1 x 3 cm) mg	Per Charge g	10
	Film layer			
	Pindolol (free base form)	15	38	
	HPC ⁽²⁾	371.95	936.3	
15	Adhesive layer			15
	NaCMC ⁽⁴⁾	31.8	80	
	F D + C Blue No 2	0.15	0.4	

PREPARATION

- 20 In analogous manner to that described in Example 3, the charge of adhesive layer components was dissolved in 3000 ml 40% ethanol. Half this charge was used to form a film layer about 1.3 mm thick (when wet) on a glass plate of dimensions 10 x 20. The plate is dried at 40°C. The remaining half of the dosage is applied. The film layer is dried again at 40°C.

- 25 The charge of film layer components is dissolved in acetone/ethanol (1:1; 4200 ml) with vigorous stirring. A quarter of the mixture is applied to the adhesive layer to provide a layer 1.3 mm thick (when wet). The new layer is dried at 40°C for 24 hours. The procedure was repeated three times using up the rest of the mixture to increase the thickness of film. The resultant two layer film is removed from the plate and cut up into oval strips (1 x 3 cm) having a thickness 1.58 mm and an average weight of 383.8 mg.

The resultant buccal strips were sealed separately in an aluminium foil.

30 THE RATE OF RELEASE OF ACTIVE AGENT IN VITRO

This was measured in analogous manner to that described in Example 3.

	Time (minutes)	Release %	
	30	13.6	
35	60	20.2	35
	120	30.5	
	180	38.6	
	240	46.1	
	300	54.2	
40	360	61.6	40

CLINICAL TRIAL

- 45 A cross-over trial was effected in 4 healthy subjects. The subjects received either 2 5 mg tablets, or a buccal strip containing on average 13 mg pindolol (as determined by analysis) applied to the interior of the mouth on the gum adjacent to the large molar teeth. Blood samples were taken $\frac{1}{2}$, 1, 1 $\frac{1}{2}$, 2, 3, 4, 6, 8, 11 and 24 hours after administration and analysed for pindolol. Urine up to 72 hours after administration was collected.

Results obtained were:—

	Tablets	Buccal strip	
	Cmax (ng ml ⁻¹)	47.2 ± 7.7	30.1 ± 3.7
	Tmax (h)	0.63 ± 0.13	4.25 ± 0.63
5	AUC 0—24 (ng ml ⁻¹)	276.3 ± 47.3	275.0 ± 52.6
	% Elimination urine	35.90 ± 5.73	24.07 ± 4.03

(AUC = Area under the curve)

A comparable total absorption of pindolol was obtained for both the tablets and buccal strip, but the buccal strip formulation showed a retardation of pindolol release.

10 CLAIMS

1. A sustained release buccal pharmaceutical composition comprising
 - (i) a non-adhesive water-soluble or -disintegrable layer,
 - (ii) an adhesive layer capable of adhering to the mucous membrane of the mouth, and
 - (iii) a medicament in at least one of said layers
- 15 characterised in that the outer surface of the adhesive layer is conformable or conforms to the shape of the mucous surface of the mouth to which the composition is to be applied.
2. A pharmaceutical composition according to claim 1 wherein the outer surface of the adhesive layer is shaped to be inwardly concave to fit onto the outside surface of the gum.
3. A pharmaceutical composition according to claim 1 or 2 wherein the outer surface of the non-adhesive layer is outwardly convex.
- 20 4. A sustained release buccal pharmaceutical composition comprising
 - (i) a non-adhesive water-soluble or -disintegrable layer,
 - (ii) an adhesive layer capable of adhering to the mucous membrane of the mouth, and
 - (iii) a medicament in at least one of said layers characterised by visual identification means in or
- 25 on the adhesive layer or non-adhesive layer.
5. A pharmaceutical composition according to any one of claims 1 to 4 wherein the adhesive layer is coloured differently to the non-adhesive layer.
6. A pharmaceutical composition according to any one of claims 1 to 5 wherein the pharmaceutical composition is in the form of a flexible strip.
- 30 7. A pharmaceutical composition according to any one of claims 1 to 5 wherein the pharmaceutical composition is in the form of a film strip.
8. A pharmaceutical composition according to any one of claims 1 to 5 wherein the pharmaceutical composition is in the form of a pressed tablet.
9. A buccal strip pharmaceutical composition comprising
 - (i) a non-adhesive polymer film layer which is porous on contact with, and wettable by, oral
 - (ii) an adhesive layer capable of adhering to the inside of the mouth, and
 - (iii) a medicament dissolved or dispersed in at least one of said layers.
- 35 10. A pharmaceutical composition according to any preceding claim wherein the non-adhesive layer is dissolvable over 5 to 24 hours in the mouth.
11. A pharmaceutical composition according to any preceding claim wherein the non-adhesive layer comprises a cellulose derivative.
12. A pharmaceutical composition according to any preceding claim wherein the non-adhesive layer comprises methylcellulose or ethylcellulose.
- 45 13. A pharmaceutical composition according to any preceding claim wherein the non-adhesive layer comprises hydroxypropylcellulose.
14. A pharmaceutical composition according to any preceding claim wherein the adhesive layer comprises sodium carboxymethylcellulose.
15. A pharmaceutical composition according to any preceding claim wherein the medicament is locally active in the mouth.
- 50 16. A pharmaceutical composition according to any preceding claim wherein the medicament is systemically active.
17. A pharmaceutical composition of any one of claims 1 to 4 wherein the medicament is pindolol.
18. A pharmaceutical composition of any one of claims 1 to 14 where the medicament is co-dergocrine.
- 55 19. A pharmaceutical composition of any one of claims 1 to 14 wherein the medicament is a calcium antagonist.
20. A pharmaceutical composition according to claim 19 wherein the medicament is 4-(2,1,3-

benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-pyridine-3,5-carboxylic acid diethyl ester.

21. A pharmaceutical composition according to claim 19 wherein the medicament is 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine-carboxylic acid isopropyl ester.

5 22. A pharmaceutical composition according to claim 19 wherein the medicament is 4-(2,1,3-benzothiadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-pyridine-3,5-carboxylic acid dimethyl ester. 5

23. A pharmaceutical composition according to any preceding claim wherein the non-adhesive layer is from 0.1 to 5 mm thick.

24. A pharmaceutical composition according to any preceding claim wherein the non-adhesive 10 layer is from 0.2 to 1.7 mm thick. 10

25. A pharmaceutical composition according to any preceding claim wherein the adhesive layer is from 0.05 to 0.5 mm thick.

26. A buccal pharmaceutical composition substantially as hereinbefore described with reference to any one of the examples.